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REVIEW ARTICLE

HMGB1 and HMGB2 proteins at the crossroads of ferroptosis, cancer, and neurodegeneration

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ABSTRACT

Introduction: High mobility group box (HMGB) proteins are nuclear DNA-binding factors that, once released from the nucleus, behave as damage-associated molecular patterns capable of activating pattern recognition receptors. The role of HMGB1 in cell death has been characterized in considerable detail, whereas HMGB2 has only lately been linked to immunogenic cell death and ferroptosis. Clarifying how these closely related proteins differentially control oxidative forms of cell death has important implications for both cancer and neurodegenerative disease.

Methods: In this review, we have assembled recent mechanistic, cellular, and translational data on HMGB1 and HMGB2 proteins with particular emphasis on studies that delineate exportin-1-dependent nuclear export, and downstream signaling networks in ferroptosis, cancer immunogenicity, and neurodegeneration. We highlight (in particular) quantitative proteomic, genetic, and pharmacologic experiments that differentiate their functions.

Conclusion: HMGB1 and HMGB2 proteins occupy distinct yet complementary, positions at the crossroads of oxidative stress, ferroptosis, and inflammatory signaling. Signaling events that depend on nuclear export of these proteins govern chemotherapy-induced immunogenic cell death in cancer as well as contributing to chronic neuroinflammation and neuronal loss. Targeting HMGB protein pathways, including exportin-1-mediated export, with novel therapeutic strategies may therefore open new avenues for cancer immunotherapy and for neuroprotective interventions.

Keywords: HMGB1; HMGB2; ferroptosis; immunogenic cell death; XPO1; cancer; neurodegeneration; calreticulin; oxidative stress; DAMP

1.0. Introduction

High mobility group box (HMGB) proteins constitute a highly conserved family of non-histone nuclear proteins that influence chromatin organization, regulate transcription, and participate in cellular stress responses[1,2]. Among the HMGB proteins, HMGB1 and HMGB2 are the most abundant and closely related, with HMGB1 sharing 93% homology and 80% sequence identity with HMGB2 (Figure 1)[3,4]. Despite this high degree of similarity, the two proteins have been interrogated very unevenly: HMGB1 has been cited roughly 17-fold more often than HMGB2, yielding a detailed picture of HMGB1 as a prototypical danger associated molecular pattern (DAMP) that engages pattern recognition receptors (PRRs), whereas the biology of HMGB2 remains comparatively underexplored[4].

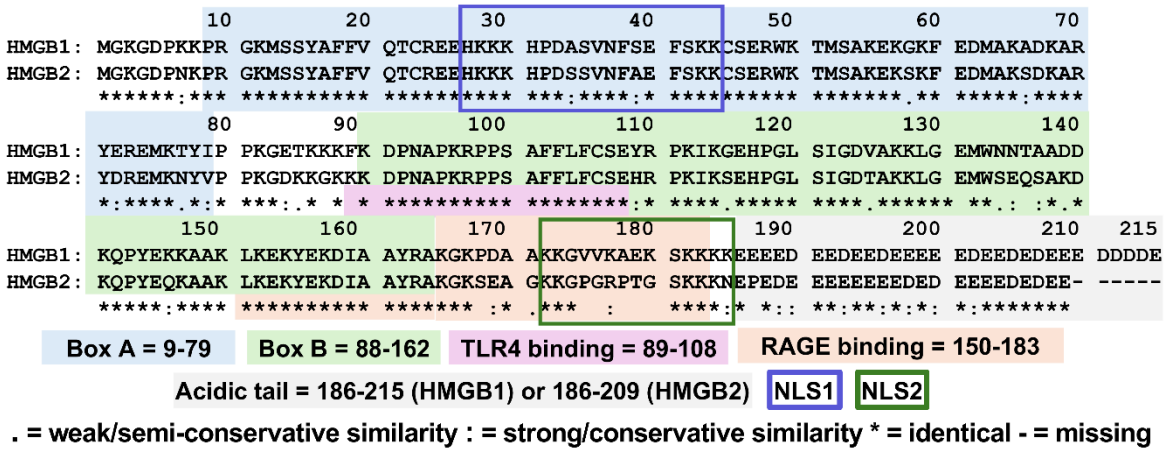

Figure 1: Alignment of HMGB1 and HMGB2 protein amino acid sequences and identification of major domains on the two proteins.

Oxaliplatin, a platinum-based chemotherapeutic, stimulates ferroptosis together with the secretion of both HMGB1 and HMGB2 from cancer cells (Figure 2). In contrast, carboplatin fails to trigger secretion of either HMGB1 or HMGB2, whereas cisplatin induces release of HMGB1 but not HMGB2 (Figure 2)[5]. These observations have yielded new mechanistic insight into how HMGBs are involved in ferroptosis and how immunologic cell death (ICD) is initiated by different platinum agents[4,6]. ICD is a regulated cell-death program that provokes adaptive immune responses against antigens from dying cells, making it highly relevant for cancer immunotherapy[7-9]. During ICD, calreticulin (CRT) must relocate from the endoplasmic reticulum to the plasma membrane to provide a crucial 'eat-me' signal to phagocytes[10], and recent data revealed that this CRT translocation requires the secretion of HMGB2, but not HMGB1[4].

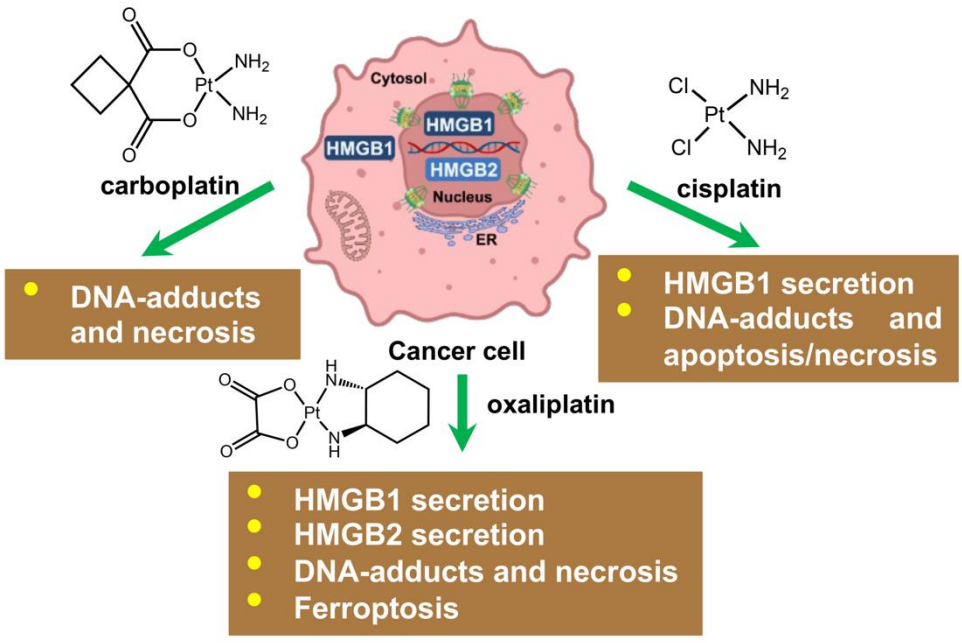

Figure 2: Platinum-mediated cancer cell death. The figure was created with BioRender.

This review synthesizes recent discoveries regarding the differential roles of HMGB1 and HMGB2 in ferroptosis, cancer biology, and neurodegeneration, with emphasis on their regulation by nuclear export mechanisms and their therapeutic implications for oxidative stress-related diseases. Therefore, we have focused the review on the

emerging roles of HMGB1 and HMGB2 as central regulators of ferroptosis and immunogenic cell death, controlled by exportin-1 (XPO1)-dependent nuclear export, in the contexts of cancer and selected neurodegenerative diseases.

2.0. Nuclear Export of HMGB Proteins via Exportin-1

XPO1 mediates the export of nuclear proteins containing leucine-rich regions that act as nuclear export signals (NES)[11]. Both HMGB1 and HMGB2 are substrates for XPO1-mediated nuclear export, and this process can be potently inhibited by the unsaturated branched-chain fatty acid macrolide antibiotic leptomycin B (Lep B) and selective inhibitors of nuclear export (SINE) compounds such as selinexor (Figure 3). Lep B contains an electrophilic α,β-unsaturated carbonyl within its lactone region that undergoes a Michael addition with a reactive cysteine (Cys528 in human XPO1) located in the NES-binding groove, irreversibly forming a covalent thioether adduct. Once covalently attached, Lep B occupies the same space that NES hydrophobic residues normally bind, effectively displacing or preventing NES peptides from engaging the groove and thereby blocking formation of the XPO1-cargo-Ras-related GTPase (Ran)-GTP export complex with an IC_{50} of approximately 10 nM[12]. Selinexor (KPT-330) also covalently modifies the reactive Cys-528 residue in XPO1's NES-binding groove, blocking the export of multiple cargo proteins with an IC_{50} of approximately 75 nM[13]. However, the covalent modification of Cys-528 in XPO1 is slowly reversible making it less toxic than Lep B[14] Inhibition of XPO1 with selinexor causes nuclear accumulation of both HMGB1 and HMGB2 in cancer cells treated with oxaliplatin, preventing their translocation to the cytoplasm and subsequent secretion into the extracellular space (Figure 3)[4]. This finding has important implications for understanding the mechanisms of chemotherapy-induced cell death and for developing combination therapeutic strategies[6].

3.0. HMGB Proteins in Ferroptosis

HMGB proteins are increasingly being recognized as important mediators of ferroptosis, a regulated cell-death modality that depends on iron-catalyzed lipid peroxidation and oxidative stress (Figure 4)[15,16]. Ferroptosis is mechanistically and phenotypically distinct from apoptosis and necrosis, exhibiting a characteristic set of morphological, biochemical, and genetic features. Core features of the ferroptotic pathway include loss of glutathione (GSH), accumulation of lipid-derived reactive oxygen species (ROS), impairment of glutathione peroxidase 4 (GPx4) activity, cellular iron overload, and attenuation of the Nrf2-driven antioxidant response program (Figure 4)[17,18].

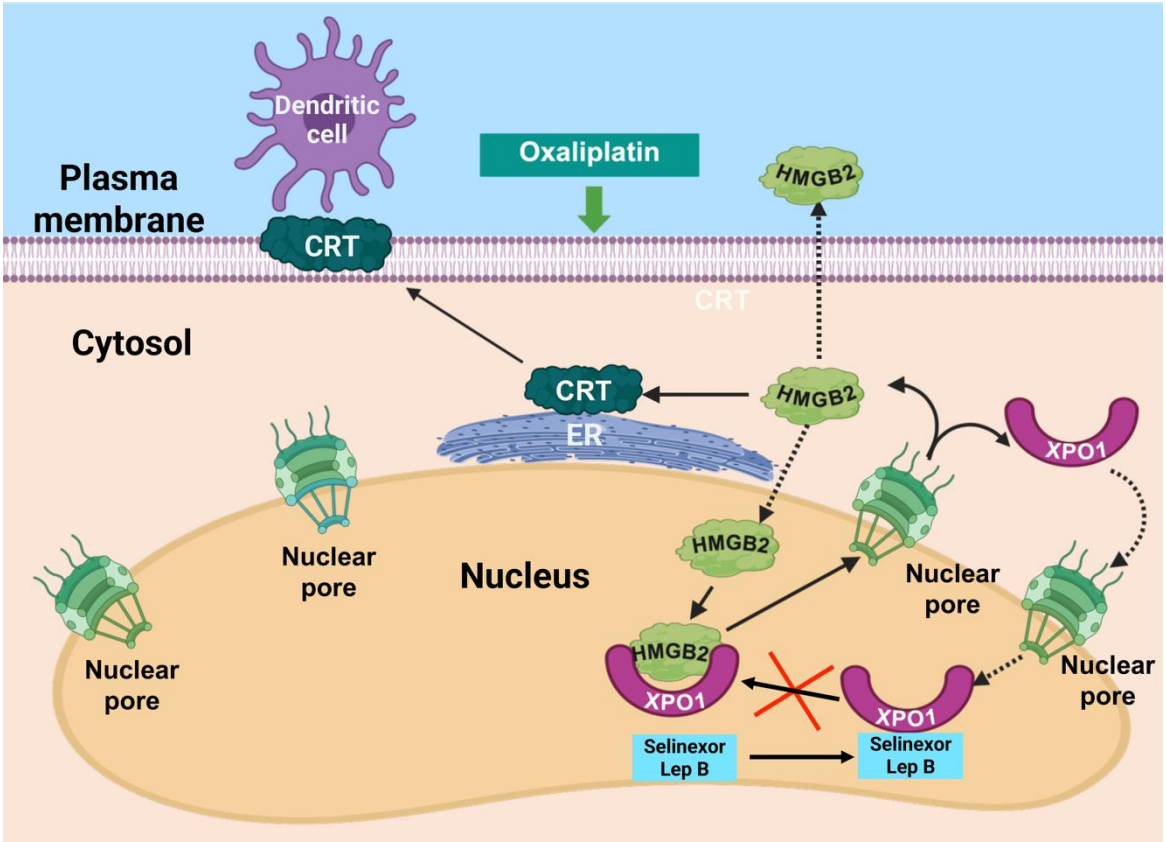

Figure 3: Oxaliplatin-induced exportin-1 (XPO-1)-mediated HMGB2 secretion from cancer cells. Secreted HMGB2 induces the translocation of calreticulin (CRT) from the endoplasmic reticulin (ER) to the plasma membrane, where it recruits dendritic cells to initiate immunologic cell death (ICD). The secretion of HMGB1 and CRT translocation from the ER are inhibited by the selective inhibitor of nuclear export (SINE) selinexor, and the unsaturated branched-chain fatty acid macrolide antibiotic leptomycin B (Lep B). The figure was created with BioRender.

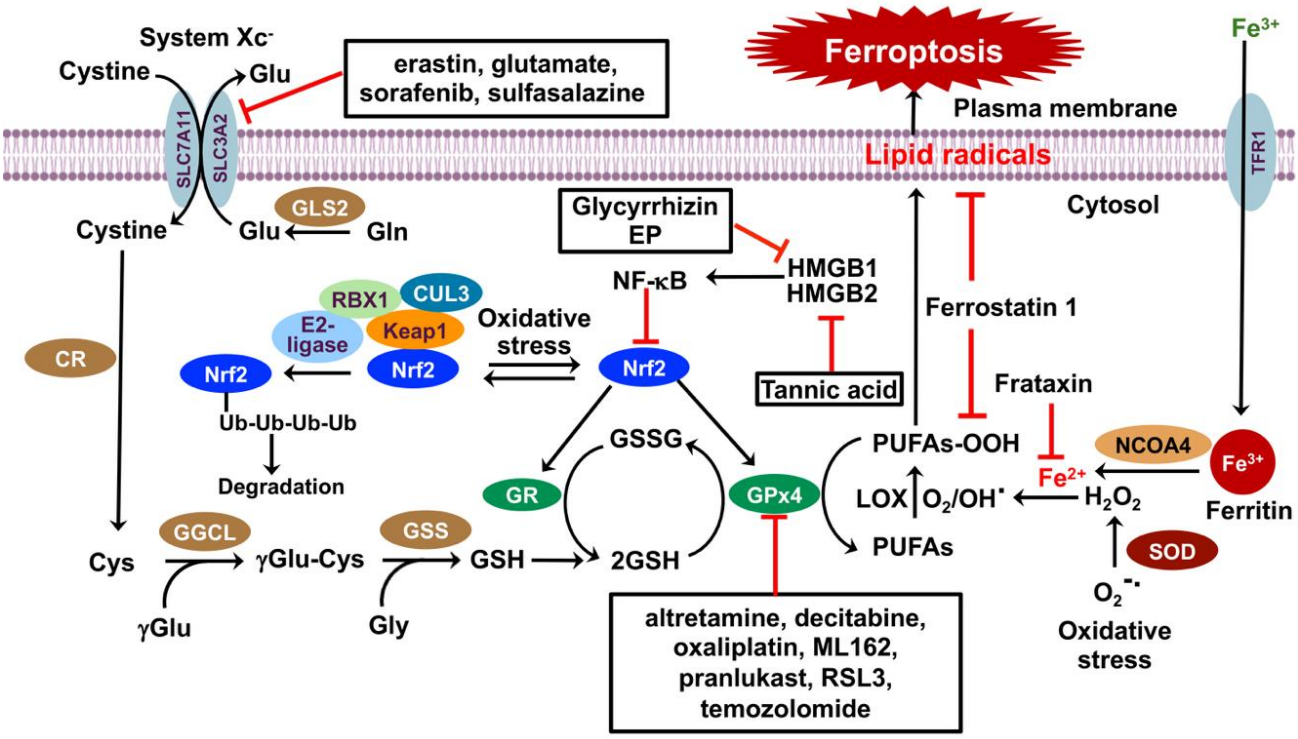

Figure 4: The role of HMGBs in ferroptotic cell death.

3.1. MECHANISMS OF HMGB-MEDIATED FERROPTOSIS

HMGB1 promotes ferroptosis through two distinct but interconnected mechanisms: autophagy-dependent ferritinophagy and autophagy-independent inflammatory signaling[19,20].

3.1.1. Autophagy-Dependent Ferroptosis Mechanisms

HMGB1 can promote autophagy through its interaction with Beclin-1 (BECN1), a central controller of autophagosome formation[21]. This interaction enhances autophagosome-lysosome fusion and cargo degradation. HMGB1-driven autophagy can engage Nuclear Receptor Coactivator 4 (NCOA4)-dependent ferritinophagy, promoting ferritin breakdown and liberation of free Fe^{2+}, which in turn amplifies ferroptosis via Fenton chemistry[22,23]. In HCT116 colon cancer cells, oxaliplatin-induced secretion of HMGB1 and HMGB2 from the nucleus was associated with multiple ferroptosis biomarkers, including increased ROS production, decreased GPx4 expression, elevated lipid peroxidation, Fe^{2+} accumulation, and reduced Nrf2 expression[4]. Importantly, inhibition of nuclear export with the XPO1 inhibitor selinexor prevented HMGB protein secretion and reversed all measured ferroptosis markers, demonstrating a causal relationship between nuclear HMGB export and ferroptotic cell death[4].

3.1.2. Autophagy-Independent Ferroptosis Mechanisms

Extracellular HMGB1 can activate inflammatory signaling through toll like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) and HMGB2 can activate TLR4, leading to nuclear factor kappa B (NF-κB) activation[24,25]. The NF-κB pathway suppresses Nrf2 expression and activity, thereby diminishing cellular antioxidant defenses and sensitizing cells to ferroptosis[26,27]. These interactions establish a positive feedback loop in which ferroptotic cells release HMGB1 and HMGB2, activating NF-κB in neighboring cells, dampening Nrf2 activity, and predisposing those cells to further ferroptotic injury. HMGB1 has additionally been implicated in neutrophil ferroptosis via signaling through the TLR4-Yes-associated protein (YAP) axis[28].

3.2. HMGB2 IN FERROPTOSIS AND CALRETICULIN TRANSLOCATION

Although HMGB1 has long been linked to ferroptosis, the distinct contributions of HMGB2 have only begun to be appreciated recently[4,25,29,30]. Oxaliplatin treatment of A549 non-small cell lung cancer (NSCLC) cells and HCT116 colon cancer cells induced dose-dependent secretion of both HMGB1 and HMGB2[4]. Importantly, HMGB2 remained in the cytoplasm only transiently; nuclear levels decreased substantially with oxaliplatin treatment, but cytosolic levels remained barely detectable, suggesting rapid secretion from the cytoplasm into the extracellular milieu. This contrasts with HMGB1, which accumulated in the cytosol of HCT116 cells following oxaliplatin treatment, indicating differential export kinetics between the two proteins[4]. A key observation is that HMGB2, but not HMGB1, robustly drives CRT translocation from the ER to the plasma membrane, a defining feature of ICD[6,8,9]. Cell-targeted HMGB2 (CT-HMGB2), engineered with a cell-penetrating TAT sequence, induced CRT translocation with remarkable potency (EC_{50} = 3.3 nM in A549 cells and 5.4 nM in HCT116 cells). This represents approximately three orders of magnitude greater potency than oxaliplatin itself. In contrast, recombinant HMGB1 did not induce CRT translocation, demonstrating a specific function for HMGB2 in this process[4]. Inhibition of XPO1-mediated nuclear export with selinexor prevented both HMGB1 and HMGB2 secretion and completely blocked oxaliplatin-induced CRT translocation, establishing that nuclear export of HMGB2 is required for this ICD-associated event.

4. HMGB Proteins in Cancer

4.1. HMGB1 IN CANCER PROGRESSION AND METASTASIS

HMGB1 influences multiple aspects of tumor biology, including growth, invasion, metastasis, and response to therapy, in a manner that depends on its localization and redox state[31]. In many settings, HMGB1 supports tumor survival by enhancing DNA damage tolerance, promoting autophagy, and sustaining a chronic inflammatory microenvironment that blunts effective antitumor immunity.

4.2. INTRACELLULAR HMGB1

In the nucleus, HMGB1 can impede the repair of cisplatin-induced DNA adducts via interactions involving its acidic tail[5,32], thereby modulating the cytotoxicity of platinum agents and other DNA-damaging therapies[33]. Nuclear HMGB1 also regulates autophagy gene expression, and its downregulation increases cancer cell apoptosis and improves treatment efficacy, consistent with a role in therapy resistance[21,34,35]. In the cytoplasm, HMGB1 engages Beclin-1 to promote pro-survival autophagy, enabling cancer cells to better tolerate metabolic and oxidative stress induced by chemotherapy, including ferroptosis-inducing regimens[36]. Cytoplasmic HMGB1 additionally contributes to mitochondrial quality control and membrane potential, processes that intersect with ROS production and susceptibility to ferroptotic cell death[31,37].

4.3. EXTRACELLULAR HMGB1

Once released, HMGB1 functions as a DAMP to activate PRRs such as TLR2, TLR4, TLR9, and RAGE on tumor and stromal cells, triggering NF-κB-dependent inflammatory signaling[38-41]. This signaling enhances production of pro-inflammatory cytokines and recruits myeloid populations that can suppress antitumor immunity, while also participating in the positive feedback loop that links ferroptotic cell death to further HMGB1 release[24,42,43]. HMGB1-driven NF-κB activation can in turn suppress Nrf2 activity, diminishing antioxidant defenses and sensitizing tumor cells to ferroptosis[24,42].

4.4. HMGB1 EXPRESSION AND CANCER PROGNOSIS

Elevated HMGB1 expression is associated with aggressive disease and poor prognosis across multiple tumor types, consistent with its roles in sustaining survival pathways and shaping an immunosuppressive microenvironment[33,44-46]. In gastrointestinal malignancies, for example, HMGB1 and its receptor RAGE are upregulated in invasive and metastatic lesions[47-49]. Targeting HMGB1 can enhance immunogenic forms of cell death such as pyroptosis, underscoring its potential as a therapeutic target in combination with ferroptosis- and ICD-inducing strategies[50].

4.5. IMMUNOGENIC CELL DEATH AND HMGB2

Some chemotherapeutic agents can cause tumor cells to die in a manner that effectively vaccinates the host, provoking adaptive immune responses against tumor antigens[51,52]. This phenomenon, now termed ICD, was first characterized by the Kroemer group, who demonstrated that anthracycline-treated tumor cells in mice elicited protective antitumor immunity[7]. The finding that HMGB2 is required for CRT translocation in oxaliplatin-treated cancer cells offers a mechanistic rationale for why oxaliplatin, but not cisplatin, robustly induces ICD, even though both agents provoke comparable HMGB1 release[4]. This finding reconciles previous observations that CRT translocation requires additional factors beyond HMGB1 secretion[53,54]. The striking difference in potency between CT-HMGB2 (EC_{50} 3-5 nM) and oxaliplatin (EC_{50} ~100 μM) for driving CRT translocation strongly argues that CT-HMGB2 itself may have therapeutic utility potential[4]. Consequently, CT-HMGB2 might be exploited as an adjuvant to boost the immunogenicity of chemotherapy-refractory tumors and to convert immunologically 'cold' tumors into 'hot' lesions that respond better to immune checkpoint blockade[55,56].

4.6. HMGB2 IN T-CELL EXHAUSTION AND IMMUNOTHERAPY

Beyond its role in ICD, HMGB2 has been identified as a key regulator of CD8+ T-cell exhaustion during chronic viral infection and cancer[57]. HMGB2 is low in naïve CD8+ T cells and becomes upregulated in effector, memory, and especially exhausted CD8+ T cells during chronic lymphocytic choriomeningitis virus (LCMV) infection, with highest levels in late exhausted cells[57]. Nuclear HMGB2 contributes to chromatin remodeling that facilitates binding of T-cell factor-1 (TCF-1) and thymocyte selection-associated HMG box (TOX), transcription factors critical for maintaining stem-like progenitor-exhausted T cells[57]. Consequently, these cells represent a reservoir that can be reactivated by immune checkpoint inhibitor (ICI therapy) to mount effective antitumor responses. A subsequent single-cell RNA-seq study in hepatocellular carcinoma revealed an $HMGB2^{+}$ CD8 T-cell subset that co-expressed inhibitory receptors. Therefore, tannic acid, (an HMGB2 inhibitor), enhanced the activity of a PD-1 antibody in attenuating tumor growth as well as reversing the T cell exhaustion[58]. Targeting HMGB2 may therefore enhance cancer immunotherapy through two complementary mechanisms: (1) Promoting ICD: secretion of HMGB2 drives CRT translocation and tumor cell immunogenicity. (2) Reversing T-cell exhaustion: Inhibiting nuclear HMGB2 levels would preserve functional CD8+ T-cells and CAR T-cells as well as enhancing responses to Programmed cell death protein 1 (PD-1)/Programmed cell death protein ligand 1 (PD-L1) blockade. This dual functionality positions HMGB2 as a particularly attractive therapeutic target for combination immunotherapy strategies.

5. HMGB1 in Neurodegeneration

5.1. HMGB1 AS A NEUROINFLAMMATORY MEDIATOR

HMGB1 has emerged as a central player in the neuroinflammatory processes underlying multiple neurodegenerative diseases[59-61]. In the central nervous system, HMGB1 is constitutively expressed in neurons[62], astrocytes[63], and microglia[64], where it performs essential nuclear functions. However, under pathological conditions, HMGB1 is released into the extracellular space, where it activates TLR4 and RAGE on glial cells and neurons, triggering inflammatory cascades[62,65].

5.2. HMGB1 IN ALZHEIMER'S DISEASE

In Alzheimer's disease (AD), HMGB1 levels are elevated in cerebrospinal fluid and brain tissue, particularly in

regions affected by amyloid-β (Aβ) plaques and tau pathology[60,66-68]. HMGB1 participates in AD pathogenesis through several mechanisms. It directly binds to Aβ and induces neurite degeneration, which can be prevented by an antibody against HMGB1[69]. HMGB1 Aβ suppresses fibril formation but increases Aβ oligomers and protofibrils[69]. Because soluble oligomeric Aβ is more synaptotoxic than mature fibrils, this HMGB1-driven shift toward oligomers is proposed to enhance synaptic dysfunction and toxicity even without changing total Aβ load[67]. HMGB1 can also activate RAGE and TLR4 to amplify inflammatory responses, so targeting HMGB1, RAGE, and TLR4 in experimental AD models has beneficial effects in halting AD progression by suppressing neuroinflammation as well as reducing Aβ load and production[67].

Emerging evidence suggests that ferroptosis contributes to neuronal death in AD[70-72]. Features of ferroptosis - including iron accumulation[73,74], lipid peroxidation,[74] and GPx4[75] downregulation - are all present in AD. HMGB1 can link Aβ toxicity to ferroptotic neuronal death through activation of NF-κB and suppression of Nrf2, reducing antioxidant defenses, promotion of ferritinophagy through autophagy induction, releasing labile iron, inducing mitochondrial dysfunction and ROS generation. The observation that inhibiting HMGB1 release with glycyrrhizin or neutralizing antibodies reduces markers of ferroptosis in AD models provides support for this potential mechanistic connection[60].

5.3. HMGB1 IN PARKINSON'S DISEASE

HMGB1 binds to aggregated α-synuclein and was found in α-synuclein filament-containing Lewy bodies in brain tissues from patients with PD and dementia with Lewy bodies[76]. This suggests that HMGB1 participates in the aggregation and propagation of pathological α-synuclein. Extracellular α-synuclein aggregates activate astrocytes and microglia, leading to chronic inflammation[77]. HMGB1 released from dying neurons can bind to α-synuclein oligomers, forming complexes that are more potent activators of inflammatory pathways than either protein alone[78]. This could create a feed-forward loop of neuroinflammation and neurodegeneration. Numerous studies have suggested that the herbicide paraquat is involved in the etiology of PD[79,80]. This has generally been ascribed to ability of paraquat to induce neuronal oxidative stress[79]. However, paraquat also increases the interaction between HMGB1 and α-synuclein in the SH-SY5Y neuronal cell model, suggestive of an additional role for paraquat in PD[81]. In addition, glycyrrhizic acid, dampened the upregulation of HMGB1 and RAGE in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTPT) mouse model of PD and decreased dopaminergic cell death in a dose-dependent fashion[82]. Dopaminergic neurons in the substantia nigra pars compacta (SNc) are particularly vulnerable to oxidative stress due to dopamine metabolism, high energy demands, and relatively low antioxidant capacity[83]. HMGB1-mediated up-regulation of NF-kB and suppression of Nrf2 (Figure 4) further compromises antioxidant defenses in these neurons, increasing their susceptibility to ferroptosis[84]. Iron accumulation is a well-documented feature of PD pathology[83], and the combination of iron overload with HMGB1-induced GPx4 downregulation (through decreased Nrf2) can drive ferroptotic death of dopaminergic neurons[18,85].

5.4. HMGB1 IN FRIEDREICH'S ATAXIA

Friedreich's ataxia (FRDA) results from reduced expression of frataxin, a protein found in mitochondria that that is required for iron-sulfur cluster assembly[86]. The resulting mitochondrial iron accumulation, impaired electron transport chain function, and increased ROS production create conditions highly favorable for ferroptosis[87]. Ferroptosis has been identified as a potential target as a novel approach to treating FRDA[88], and so the potential role of HMGB1 in this devastating disease warrants investigation. It is noteworthy that over-expression of frataxin can prevent glutamate-induced ferroptosis in SH-SY5Y neuronal cells[89] and that frataxin regulates ferroptosis in human fibrosarcoma cells[90], in keeping with the concept that a deficiency of frataxin protein in FRDA pre-disposes cells to ferroptosis[88].

6. Conclusions

The emerging understanding of HMGB1 and HMGB2 as critical regulators of ferroptosis, cancer biology, and neurodegeneration represents a significant advance in our knowledge of oxidative stress-related diseases. Collectively, recent studies support several key conclusions:

1. **HMGB1 and HMGB2 have distinct functions:** While structurally similar, HMGB2 uniquely induces CRT translocation required for ICD, whereas HMGB1 serves broader roles in inflammation and stress responses.
2. **Nuclear export via XPO1 is central to HMGB function:** Both HMGB1 and HMGB2 are exported from the nucleus by XPO1, and inhibiting this export prevents downstream effects on ferroptosis and immunogenic cell death in cancer models.
3. **HMGB proteins mediate ferroptosis through multiple pathways:** These include autophagy-dependent ferritinophagy, NF-κB-mediated Nrf2 suppression, and TLR4-YAP signaling that enhances iron uptake and lipid peroxidation.
4. **Therapeutic strategies must be tailored to context:** Promoting HMGB-driven ferroptosis and secretion may be advantageous in oncology, whereas dampening these pathways is more likely to yield neuroprotective effects in degenerative conditions.
5. **CT-HMGB2 represents a novel immunotherapy approach:** The extraordinary potency of cell-targeted HMGB2 in inducing CRT translocation suggests potential for converting immunologically "cold" tumors into "hot" tumors responsive to checkpoint inhibitors.
6. **HMGB1 neutralization offers neuroprotective benefits:** In preclinical models of AD and other neurodegenerative conditions, blocking HMGB1 signaling reduces DNA damage propagation, preserves synaptic function, and improves cognitive outcomes.

The field now stands at an exciting juncture where mechanistic insights are being translated into therapeutic strategies. Emerging XPO1 inhibitors, HMGB-directed biologics, pharmacologic modulators of ferroptosis, and rational combination regimens together offer a promising framework for improving outcomes across cancers, neurodegenerative disorders, and other diseases driven by oxidative stress.

7.0. Acknowledgments

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